

Optimal nutrition and its potential effect on survival in critically ill patients

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ABSTRACT

Optimal nutrition serves to maintain normal organ function and to preserve body energy stores to guarantee survival during times of shortage of food. Especially total body protein content is an important determinant of survival. However, recommendations about nutrition refer mostly to total energy intake with either no emphasis on total protein content or protein intake only considered as a fixed percentage of caloric intake.

This paper focuses on the role of total body protein mass or lean body mass (= mass of organs and muscle) (LBM) on survival of healthy humans and critically ill patients. Recommendations on the amount of protein per kg bodyweight are made based on the scarce evidence available in humans.

to energy intake with either no emphasis on protein content or protein intake only considered as a fixed percentage of caloric intake (usually 15%).

This review focuses on protein mass or lean body mass (= mass of organs and muscle) (LBM). Lower body mass index (BMI) values have been related to low LBM, a condition associated with increased mortality.¹ This is easily understandable because proteins are involved in almost all metabolic processes. Although this seems a reasonable statement, its proof is less certain. Data on this issue are scarce for obvious reasons. Observations on the relation between protein mass and mortality are biased by comorbidity which can/will influence time of death. Observations on the relation between protein mass and mortality in otherwise healthy subjects are extremely rare.

KEYWORDS

Lean body mass, protein content, diet, critical illness, mortality

OPTIMAL NUTRITION

Nutrition is often referred to as the adequate amount of energy intake with a fixed composition of macronutrients (35% fat, 50% carbohydrates and 15% protein). The optimal goal of nutrition is survival during times of shortage of food with fat mass and total body protein mass being the most important determinants, but for short-term survival replenishment of carbohydrates is sufficient. This demonstrates that optimal nutrition depends on the actual circumstances and therefore cannot always be simplified in a standard menu. However, recommendations about nutrition refer mostly

LOSS OF LEAN BODY MASS DURING STARVATION

Observations in Irish and Turkish hunger strikers have shown that they die ~60 days after a complete fast without water restriction, while having lost 40 to 50% of their bodyweight. Observations in famine victims report a minimum BMI of 10 kg/m² to be required for survival.^{2,3} Detailed body composition studies have not been done, but from the rate of loss of each body compartment during semi-starvation reasonable assumptions can be made. The most comprehensive studies have been done by Keys, in his classical 'Minnesota Experiment', which documented on body composition during weight loss in healthy young men on a six-month hypocaloric diet of 40% of their daily energy need. After three months, the subjects had lost around 50% of their body fat and 20%

of their LBM. After six months, the losses were 70% and 28% respectively.⁴ Studies with (very) low calorie diets confirm this observation.²

Calculations from data obtained in various studies in hunger strikers show that on the third day and thereafter ~20% of the energy loss was derived from protein catabolism, resulting at death in the virtual absence of fat depots, whereas the loss in LBM was less than 50%.² The fraction of LBM lost when the fat stores reach total depletion represents the dispensable component of the protein compartment that is compatible with life. This corresponds with a BMI of $\approx 10 \text{ kg/m}^2$.² These observations suggest maintenance of protein mass above a critical minimum to be more important for survival than maintenance of fat mass.

In conclusion, a critical amount of LBM is essential for the body to function in a vital manner. Data from hunger strikers show that a loss of total body protein of more than 40%, corresponding with a BMI of approximately 10 kg/m^2 , is not compatible with life.

PROTEIN MASS AND MORTALITY IN CRITICAL ILLNESS

The question arises whether a comparable relation between protein mass and mortality exists in critically ill patients. Studies on this issue are by definition observational, as intervention studies are unethical. Studies on the exact relation between total body protein mass and mortality in critically ill patients do not exist, as *accurate* measurement of protein mass (only via *in vivo* neutron activation analysis) in critically ill patients is extremely difficult. In addition, this research tool is available at only very few centres worldwide. It provides a noninvasive analysis of the total body content of major molecules (calcium, nitrogen, sodium, oxygen, hydrogen, and carbon). It is based on the principle that each atom is capable of undergoing nuclear reactions when exposed to neutrons. The excited atom releases energy in the form of gamma rays which is specific for each atom and can be detected and counted with a gamma counter. Because there is a fixed relation between nitrogen and protein [protein (g) = $6.25 \times$ nitrogen (g)], total body protein can be calculated from measured total body nitrogen. This is considered the gold standard for estimating total body protein.⁵

This problem is due to the fact that protein content and LBM are not completely interchangeable concepts. The constant relation between lean body mass and protein content, found in healthy subjects, is disturbed in critically ill patients due to changes in intracellular water content. BMI is sometimes used as a surrogate marker of LBM, although it is well known that the correlation between BMI and LBM is not very tight, in the higher ranges

especially.⁶ However, in general a low BMI approximates to low weight, fat mass and fat-free mass.⁷ Observations in large groups of critically ill patients indicate that a low BMI is an independent risk factor for mortality. It increased as a continuous variable down to a BMI of 15 kg/m^2 in 1488 mechanically ventilated adults with acute lung injury.⁸ These data are not in contradiction to a study in over 40,000 critically ill patients, showing excess mortality only in patients with a BMI $< 20 \text{ kg/m}^2$.⁹

In conclusion, data from critically ill subjects suggest that the size of the dispensable part of the protein component is not different from that in healthy subjects. In other words, loss of a significant amount of body protein has the same influence on mortality in critical illness as it has in otherwise healthy subjects during starvation.

MAXIMAL STIMULATION OF WHOLE BODY PROTEIN SYNTHESIS AND MAINTENANCE OF PROTEIN MASS

The size of total protein mass is determined by the balance between protein synthesis and protein breakdown. Under normal circumstances in healthy volunteers, whole body protein breakdown after an overnight fast is greater than protein synthesis, resulting in a negative protein balance. After a meal protein synthesis is stimulated and nitrogen balance becomes positive. This situation will remain for a few hours after the meal. After that period, the balance gradually becomes negative again, until a new meal is consumed. The net effect of these fluctuations in fasting and feeding during the day is a zero-balance.^{10,11}

The capacity to synthesise protein from meal-derived amino acids is limited. The maximum capacity of protein synthesis on whole body level is reached with a protein intake of 1.5 g/kg/day in healthy volunteers as well as in critically ill patients.¹²⁻¹⁴ Insulin slows down the rate of protein breakdown and augments the effects of amino acid delivery on the synthesis of protein,¹⁵ suggesting that its combination with sufficient amino acids in an anabolic state provides the best basis for optimal nutrition. However, before implementing this viewpoint, the following question is relevant: Is $1.5 \text{ g protein/kg/day}$ really the amount that best maintains whole body protein mass in patients? In such a study, whole body protein content should be determined in a reliable way. The gold standard is the *in vivo* neutron activation analysis (see above). At this moment, we are aware of only two studies that have used this technique in critically ill patients. One study was carried out in surgical patients after major abdominal surgery, which reported that a mean provision of 0.9 g protein/kg preoperative body weight/day proved to be insufficient to preserve muscle mass and prevent nitrogen loss, whereas

body protein mass was conserved when 1.6 g protein/kg preoperative bodyweight/day was given.¹⁶ The other study was a retrospective analysis carried out in critically ill sepsis and trauma patients. Due to overhydration of most patients, the protein amount was indexed to normally hydrated corrected fat free mass which resulted in a protein amount of either 1.1, 1.5 and 1.9 g of protein/kg fat free mass during 14 days.¹⁷ Provision of 1.5 g protein/kg fat free mass proved the optimal amount to preserve protein mass. This amount corresponded with 1 g protein/kg actual total body weight/day. The authors conclude that for critically ill patients the optimal nutrition is 1 g protein/kg actual bodyweight or 1.2 g protein/kg pre-admission bodyweight/day. This difference in recommendation relates to overhydration of most critically ill patients. Whether 1.2 g protein/kg/day would have been as effective as 1.6 g protein/kg/day in the surgical patients has not been studied, but a difference between mechanically ventilated and immobilised ICU patients and mobile patients on a surgical ward can be expected. Muscle contractions are essential for sustaining muscular mass. For instance, in healthy volunteers subjected to full immobilisation for four to five weeks, the nitrogen balance becomes negative despite an intake of 90 g protein and 2700 kcal.¹⁸

In conclusion, to maintain total body protein mass 1.5 g protein/kg preadmission bodyweight/day in patients in general and 1.2 g protein/kg preadmission bodyweight/day in ICU patients could be used as a target for providing adequate nutritional therapy.

EFFECT OF ADMINISTRATION OF OPTIMAL PROTEIN ON MORTALITY IN CRITICAL ILLNESS

Guidelines have proposed optimal nutrition for patients admitted to the intensive care to be the provision of energy as determined by indirect calorimetry, and a protein content of at least 1.2 g/kg preadmission weight per day.¹⁹ In one of the scarce prospective studies evaluating this approach in 283 medical-surgical ICU patients, women who reached their nutritional goals had a significantly lower hazard ratio of dying on the ICU as well as lower 28-day mortality. This benefit on mortality was not present in women reaching their energy target whilst not reaching the protein target. In men, no statistically significant effects of nutrition on outcome could be detected. This difference was ascribed to a gender-related difference in body composition with larger absolute protein stores in men.²⁰ No studies have been published on gender-related minimal protein mass decisive for survival. When this mass is an absolute one and not related to bodyweight, males have an advantage in nutritional reserve, because of larger absolute protein stores. This will protect them

longer from reaching the absolute threshold of minimal body protein needed to guarantee normal organ function. Another explanation could be related to the calculation of protein per kg bodyweight instead of per kg fat free mass. Women have a lower percentage of fat free mass per kg bodyweight and therefore in that study received a higher amount of protein per kg fat free mass which may be beneficial for survival.

This manuscript focuses on optimal protein content in nutrition of critically ill patients. Caloric need was defined in a national guideline on perioperative nutrition.²¹ This guideline defined energy need as the amount of energy calculated with the Harris and Benedict 1984 formula + 30%. For long-term patients in the intensive care unit, the guideline advocated tailoring energy provision towards resting energy expenditure determined by indirect calorimetry + 10%. Caloric need and required macronutrients differ between healthy subjects and critically ill patients as shown in *table 1*. Recently it has been shown that implementation of guidelines and evidence on nutrition can be ameliorated by using an algorithm with an advice module available on-line.²²

Table 1. Recommendation for required macronutrients for healthy subjects²³ and critically ill subjects not admitted to ICU, based on a caloric need of 1800 kcal/day in a 70 kg subject, expressed in absolute amounts and as percentage of energy expenditure. Caloric need was estimated as equal for both groups, as in general the increase in oxygen consumption induced by critical illness is equalised by its lack of physical exercise

	Healthy subjects	Critically ill subjects
Energy expenditure (kcal/day)	1800	1800
Protein (g/day)	56	105
Carbohydrate (g/day)	250	250
Fat (g/day)	65	40
Energy expenditure (kcal/day)	1800	1800
Protein (kcal/day)	225	420
Carbohydrate (kcal/day)	1000	1000
Fat (kcal/day)	575	380

CONCLUSION

Maintenance of protein mass in critically ill patients above an (absolute?) value is mandatory for influencing survival. The optimal amount of protein is 1.2 g/kg preadmission bodyweight/day in critically ill septic and trauma patients. For surgical non-ICU patients, it has been shown that 1.6 g protein/kg preadmission bodyweight/day was able to prevent nitrogen loss and preserve muscle mass. In combination with

earlier studies showing that whole body protein synthesis is maximally stimulated during intake of 1.5 protein/kg body weight/day, we recommend 1.5 protein/kg body weight/day as optimal for non-critically ill patients. More evidence is needed to study the effect of some of these nutrition goals on outcome.

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